

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

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| Applicant's or agent's file reference IPB/130246 | FOR FURTHER ACTION | See item 4 below |
| International application No. PCT/DK2005/000094 | International filing date (<i>day/month/year</i>) 11 February 2005 (11.02.2005) | Priority date (<i>day/month/year</i>) 19 February 2004 (19.02.2004) |
| International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237 | | |
| Applicant CHEMINOVA A/S | | |

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).
2. This REPORT consists of a total of 7 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|---|
| <input checked="" type="checkbox"/> | Box No. I | Basis of the report |
| <input type="checkbox"/> | Box No. II | Priority |
| <input type="checkbox"/> | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> | Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> | Box No. VI | Certain documents cited |
| <input type="checkbox"/> | Box No. VII | Certain defects in the international application |
| <input checked="" type="checkbox"/> | Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

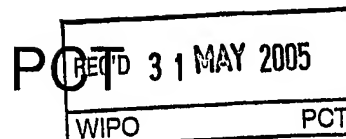
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| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland | Date of issuance of this report 22 August 2006 (22.08.2006) |
| Facsimile No. +41 22 338 82 70 | Authorized officer <div style="text-align: center; font-weight: bold;">Simin Baharlou</div> e-mail: pt09@wipo.int |

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220



WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/DK2005/000094

International filing date (day/month/year)
11.02.2005

Priority date (day/month/year)
19.02.2004

International Patent Classification (IPC) or both national classification and IPC
C07B39/00, C07B53/00, C07C45/63, C07F7/18

Applicant
HALLAND, Nis

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1b/s(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/DK2005/000094

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/DK2005/000094

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|-------------|---------------|
| Novelty (N) | Yes: Claims | 1-13,15,16,17 |
| | No: Claims | 14 |
| Inventive step (IS) | Yes: Claims | 1-13,15,16,17 |
| | No: Claims | 14 |
| Industrial applicability (IA) | Yes: Claims | 1-17 |
| | No: Claims | |

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V.

1 Reference is made to the following documents:

D1 : LUKAS HINTERMANN AND ANTONIO TOGNI: "Catalytic Enantioselective Chlorination and Bromination" HELV. CHIM. ACTA, vol. 83, 2000, XP002327583

D2 : MARTIN OSTENDORF ET AL.: "(S)-Pyroglutamic Acid, (S)-Malic Acid, and (S)-Serine as Useful Starting Materials in the Synthesis of Enantiopure Hydroxyamidines" EUR. J. ORG. CHEM., vol. 2000, no. 1, 2000, pages 115-124, XP002327582

D3 : LEUTENEGGER U ET AL: "5-Aza-Semicorrins: A New Class of Bidentate Nitrogen Ligands for Enantioselective Catalysis" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 48, no. 11, 1992, pages 2143-2156, XP002087673 ISSN: 0040-4020

2 INDEPENDENT CLAIM 1

2.1 The present application meets the criteria of Article 33(1) PCT with respect to claims 1-13, because the subject-matter of said claims is new and inventive in the sense of Article 33(2) and 33(3) PCT.

2.2 Document D1, which is considered to represent the most relevant state of the art, discloses a catalytic enantioselective process for the α -bromination and α -chlorination of β -keto esters. The halogenating agent is either NBS or NCS (N-bromosuccinimide or N-Chlorosuccinimide). The catalyst used is a chiral Ti(TADDOLato) complex. The catalyst used is therefore a chiral inorganic compound. In Scheme 4, β -keto ester 3a-e is either chlorinated or brominated in the presence of this catalyst. The difference of this disclosure and the subject-matter of the present application is that in the present application instead of an inorganic compound, a nitrogen containing organic compound is used. The problem to be solved by the applicant was to provide an alternative solution for the catalytic enantioselective halogenation of an α -keto compound of formula (2). Starting from D1, a skilled person would not substitute the Nickel complex by a chiral nitrogen containing compound as he would not have an incentive in D1 or elsewhere in the prior art to do so. It is therefore considered that independent claim 1 and its dependent claims 2-13 are inventive over the prior art.

3 INDEPENDENT CLAIM 14 - Novelty (Article 33(2) PCT)

- 3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 14 is not new in the sense of Article 33(2) PCT. Document D2 discloses compound 10 which falls within the scope of claim 14 of the present application. Claim 14 is therefore not novel over D2.
- 3.2 Document D3 discloses in Scheme 2 the preparation of (S)-5-[(tert-Butyl)dimethylsilyloxy]methyl-2-pyrrolidinone (product formed after silylation of alcohol 7. This compound is novelty destroying for claim 14 of the present application.
- 3.3 Claims 15-17 are novel over the prior art. The compounds of claims 15-17 are used in the novel and inventive process of claim 1. The inventive feature of claim 1 of the present application is the use of chiral nitrogen containing organic compound. The compounds of claim 15-17 are examples of such chiral nitrogen containing organic compounds. The subject-matter of claims 15-17 is therefore considered inventive over the prior art with respect to Article 33(3) PCT.

Re Item VIII.

4. Clarity (Article 6 PCT)

- 4.1 The application does not meet the requirements of Article 6 PCT, because claims 2-13 are not clear.

In the said claims the definition of R, R1 and R2 are given. One of the radicals mentioned is C1-10 alkyl. In the description it is said on page 3 that alkyl also comprises cycloalkyl. This is usually not the case for this definition as it normally means aliphatic branched or linear saturated groups. Such a definition in the said claims renders the scope unclear as a skilled person would not assume that cycloalkyl is within the scope of alkyl.

Claim 4, amongst others, refers to the definition "alkylaryl group". It is normally understood by a skilled person as an aryl radical which is substituted by an alkyl group. In the description on page 4 it is however an alkyl radical, substituted by an aryl group.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/DK2005/000094

Such a definition in the claims renders the scope unclear.